CALCIUM METABOLISM, WITH SPECIAL REFERENCE TO EXOPHTHALMIC GOITRE.

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In recent years much attention has been paid to the inorganic salts of the body, and many metabolism records of health and disease include estimations of calcium and magnesium and some of sodium and potassium. Besides the consideration of the metabolism phenomena, the pharmacological effect of the minerals and the mineral content of the tissues has been studied. The result of this widespread interest has been the accumulation of a large amount of material. No large work has been inaugurated in this field as was done by the United States Government in the case of nitrogen, and general principles must be deduced from a consideration of all the work collected. Calcium occurs in sufficiently large quantities to make the necessary error of all metabolism work a small percentage of the whole amount, and the process of quantitative estimation is not difficult; hence, the number of calcium records available as compared with those of other minerals is large. The special problems of metabolism, absorption, equilibrium, etc., are as indefinite with reference to calcium as uncorrelated results can make them. For this reason, and because the results of my own experiments can only be interpreted by a comparison with those of others, it seemed necessary to sum up as briefly as possible the work which has been done on these points.

In regard to the degree of absorption there is an insuperable difficulty. Voit[1] found, when he fed an animal on a diet containing a small amount of calcium, that he obtained more calcium in the feces than was contained in the food; he concluded that calcium was excreted by the intestinal wall. The import of this finding was more fully understood when Rey,[2] having cleared the intestinal canal of animals, gave subcutaneous injections of a calcium salt; he learned by this method that the amount excreted by the intestinal wall might reach over 50 per cent. of the intake, but that the variation was great. There remains the consideration of the balance obtained by deducting from the calcium intake the urinary and gross fecal output without reference to the part of this which is used in the body processes. This balance has been found to be affected by the following conditions: (1) Underfeeding or overfeeding with reference to the physiological requirement; (2) starvation; and (3) pathological conditions.

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[1] Ztschr. f. Biol., 1880, xvi.

[2] Arch. f. exp. Path. u. Pharm., 1895, xxxv.

The physiological requirement has been estimated variously. Bunge[3] thought that 3.3 grams CaO was necessary each day; Bertram[4] found himself in equilibrium at 0.38 gram CaO for the two days which he followed his metabolism; more recently Renvall[5] did an experiment on himself covering a period of fifteen days; this is the longest and most convincing record of calcium metabolism in a normal person. Taking 0.85 to 0.9 gram CaO a day, Renvall found that there was a daily variable loss or gain in the hundredths of a gram; since he weighed 62 kilograms, this gives 0.014 gram CaO per kilo of body weight each day for an adult.

A large amount of work has been done on underfeeding in animals; since rickets and osteomalacia were the most striking examples of calcium disturbance in human pathology, it was natural that they should be the objective point of experimental work. In 1880 Voit was able to accomplish what others had tried with varying success. He reduced the calcium intake of puppies to its lowest terms, and found that after a period of from one to four months, depending on the size of the breed of dog used, the muscle and fat were normal; but the bones were vascular, porous, fractured and fissured in places, and the teeth were imperfect. His calcium-poor diet contained about 0.05 gram CaO daily, and the normal 0.7 gram CaO each day. Though he thought he had produced rickets experimentally, later work showed that there were important differences between the two conditions; but he did show that in the growing organism the lack of calcium is felt most by the bones. Goitein[6] found the physiological requirement of a rabbit to be 0.16 gram CaO per kilo of body weight daily. He concluded from the results he obtained when he varied this amount that with a calcium-poor diet there was a calcium loss, and with a calcium-rich diet there was a calcium retention. The first half of this conclusion for rabbits has been sustained for human beings in calcium underfeeding by the work of von Wendt.[7] He found that a constant loss of calcium up to 0.1 to 0.2 gram a day accompanied a diet containing 0.05 to 0.1 gram daily. Müller[8] and his colleagues found that the calcium output of a starving man was greater than the calcium content of the drinking water.

The subject of calcium overfeeding has been approached by the following workers: Bertram (1897) took 30 grams of the carbonate; he recovered it partly, unchanged in the feces, which showed white with the grains of the salt contained. Herxheimer[9] (1897) also observed himself, and took the carbonate, 18 grams for five days, and 6 grams for the following three days, in the form of a bread

[3] Albu, Neuberg, Mineralstoffwechsel.

[4] Ztschr. f. Biol., 1878, xiv.

[5] Skand. Archiv f. Phys., 1904, xvi.

[6] Archiv f. d. gesamt. Phys., 1906.

[7] Skand. Archiv f. Phys., 1905.

[8] Ztschr. f. Biol., xx; Virchow's Archiv, 1893, cxxxi.

[9] Berl. klin. Woch., 1897, No. 20.

that was manufactured for metabolism disorders. He found a retention of 15.9 grams CaO in the eight days of the experiment. Kaufmann and Mohr[10] (1903) obtained the calcium balance of two patients in the hospital who had no demonstrable lesion. Milk was given in addition to other things, and the calcium intake in one case was 6 grams CaO and in the other 4.4 grams daily. The former retained 16 grams in seven days and the latter 20 grams CaO in ten days. Renvall (1904), in an experiment on himself, used the carbonate in small doses; after the fifteen days of normal metabolism record, referred to under the physiological requirement, he began with 0.5 gram of the carbonate, and retained steadily and continued to do so when he increased the amount to 1 gram. He reached equilibrium about seventeen days after he began to take the carbonate. Thus, the latter half of Goitein's conclusion is supported by four experiments on human beings; a calcium-rich diet (one containing over 2 grams CaO a day) is followed by a calcium retention.

Before passing to the consideration of pathological conditions, one other point must be mentioned which seems, in the few cases in which it has been tried, to affect the calcium balance. The addition of sodium chloride in any appreciable amount appears to increase the calcium output. This is shown by Marischler's[11] work in nephritis and Moraczewski's[12] in carcinoma. The former followed the metabolism of 7 cases of nephritis for nine days each; he divided the whole time into periods of three days each, and gave 6 grams NaCl daily on the second set of three days. In 5 of the 7 cases there was an immediate drop in the calcium retention, or a small retention was converted into a loss. The latter added 10 grams NaCl to the diet of a patient having carcinoma; the calcium balance became negative, though it had been positive on the same calcium intake before the NaCl administration was begun. He obtained a different result in his case of chlorosis, but the NaCl period here followed the administration of so many other salts that the picture is not clear. The pathological conditions have been studied almost entirely from the standpoint of calcium overfeeding, not so much intentionally as because this is an accompaniment of the milk diet, which is both an easy form of nutrition for metabolism work and indicated in many forms of disease.

Rumpf[13] (1897) obtained the calcium balance of a girl, aged nineteen years, who had a stomach ulcer. She was on a milk diet, and received 3.3 grams CaO a day; she retained 1.8 grams CaO daily.

Moraczewski[14] (1901) found a constant negative balance in a case of diabetes with an intake of 1.6 grams CaO a day in the food.

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[10] Berl. klin. Woch., 1903, No. 8.

[11] Archiv f. Verdauungsk., 1901.

[12] Zeit. f. klin. Med., 1898, xxxiv.

[13] Berl. klin. Woch., 1897, No. 13.

[14] Zeit. f. klin. Med., 1897, xxxiii.

He changed this to a positive balance by adding 10 grams of the phosphate of calcium and bringing the whole intake up to 5.3 grams a day; the withdrawal of the phosphate was immediately followed by a loss which was a second time counteracted by administering the phosphate, this time in smaller doses; in five days, with an intake of 2.3 grams daily, there was a retention of 2.15 grams.

Ott[15] (1901) worked with phthisical subjects, and found a positive balance in 7 out of 8 cases.

Hirsler and von Terray[16] (1905) followed a case of endo-arteritis, a male, aged fifty-seven years. They divided a six-day period into two of three days each; they gave milk in the first period and added bone meal in the second; the patient retained 3.9 grams CaO in the first three days and 5.3 grams CaO in the second period.

King[17] (1907) followed the metabolism of a case of arthritis deformans; the Folin diet was used, and found to contain an average of 4.6 grams CaO in a day; in the five days of the experiment there was a retention of 9.6 grams CaO.

A calcium loss was found in diabetes by both Moraczewski and Gerhardt and Schlesinger;[18] in the latter work at least there was a coincident factor, which occurs in other pathological conditions, and has always been found to be accompanied by a calcium loss; that is, acidosis. Besides this work of Gerhardt and Schlesinger's there is the record of a case of acidosis of unknown origin obtained by Barker and Voegtlin;[19] in this case there was a high organic acidity, and the chief output was through the intestine. Falta and Whitney,[20] after the extirpation of the pancreas of a dog, found an increase of the output of the calcium in the urine. The ammonia was not estimated, but the uric acid rose considerably, and a state of acidosis seemed likely, due either to the removal of the pancreas or to a postoperative acidosis. Some work has been done on the administration of acid by the mouth. Rüdel[21] gave dilute hydrochloric acid to a child and obtained an increase of the calcium of the urine; later, he gave concentrated HCl to a dog, and found a still greater increase of the output of CaO. Gaehtgens[22] observed a dog for nine days, and in the second group of three days gave sulphuric acid; the ammonia rose to three times its former value, and the urinary calcium was increased. He quotes Kurtz as having given sulphuric acid and having a general increase in the output of the salts; potassium was the one most affected, but calcium, magnesium, and sodium were all increased. The ratio of the urinary and fecal output of calcium has always been of interest, though it is of limited significance as an indication of the degree of absorption. By arranging the results of the metabolism work in the form of a table, we see that on an intake of 4 to 6 grams CaO daily the fecal output ranges beteeen 85 per cent. and 95 per cent. of the whole output; the exceptions to this are King's case of arthritis and one of the cases of chlorosis in which it was 70 per cent. Renvall showed a high urinary output up to the time he began to take the carbonate; in the first two periods 60 per cent. and 64 per cent. were excreted through the kidneys. In Gerhardt's case of diabetes, in the period in which the acidosis was not combated by the alkali, the urinary output of calcium rose to 73 per cent. of the whole output. There is a certain amount of agreement between the cases on an intake of 1 to 2 grams CaO daily; many of them have approximately 60 per cent. of the output fecal and 40 per cent. urinary. This is, however, by no means universal; all the carcinomas and several of the chlorotic cases differ from it very markedly.

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[15] Deutsch. Archiv f. klin. Med., lxx, and Zeit. f. klin. Med., l.

[16] Zeit. f. klin. Med., 1905, lvii.

[17] Johns Hopkins Hosp. Bull., June-July, 1907.

[18] Arch. f. exp. Path. u. Pharm., xlii. [19] Johns Hopkins Hosp. Bull., June-July, 1907.

[20] Beitr. z. chem. Phys. u. Path., 1908.

[21] Arch. f. exp. Path. u. Pharm., 1894, xxxiii.

[22] Zeit. f. phys. Chem., 1880.

Table I.

Author.	Daily intake in grams CaO.	Urinary per cent.	Fecal per cent.	Author.	Daily intake in grams CaO.	Urinary per cent.	Fecal per cent.
Van Wendt	Normal, 0.05	10.0	90.0	Mayer	Phthisis, 1.5	40	60
"	" 0.2	21.0	79.0	"	" 2.0	37	63
Renvall	" 0.85	60.9	39.1	Moraczewski	Carcinoma 10 gms. $Ca_2(PO_4)$	11	89
"	" 0.9	64.3	35.7	"	Carcinoma, 1.3	13	87
"	" 0.9	29.1	70.9	"	" 1.3	6	94
"	" 0.9	36.1	63.9	"	" 1.3	9	91
"	" 0.9	25.4	74.6	"	" 1.3	12	88
Herxheimer	" 11.6	7.5	92.0	"	" 2.9	5	95
"	" 3.7	12.4	87.0	"	" 0.9	71	29
Kaufmann and Mohr	" 6.0	8.0	92.0	"	Chlorosis, + 10 gms. $Ca_3(PO_4)$	29	71
" "	" 4.5	8.0	92.0	"	Chlorosis, + 10 gms. $Ca_3(PO_4)$	11	89
King	Arthritis, 4.5	30.5	69.5	"	Chlorosis, 0.9	20	80
Barker and Voegtlin	Acidosis	14.3	85.7	"	" 1.3	40	60
Gerhardt and Schlesinger	Diabetes, 0.8	38.0	62.0	"	" 0.9	40	60
" "	" 0.8	73.0	26.0	"	" 0.9	40	60
" "	" 0.8	55.0	45.0	"	" 1.4	9	91
Hirsler and v. Terray	Arteriosclerosis, 5.8	6.9	93.1	"	" 1.4	39	61
" "	" 7.2	7.4	92.6	"	" 0.9	9	91
Ott	Phthisis, 4.4	5.0	95.0	"	" 1.4	4	96
"	" 6.1	13.0	87.0	"	" 1.4	9	91
"	" 6.0	6.0	94.0	"	" 1.4	19	81
"	" 4.5	7.0	93.0	Towles	Hysteria, 0.3	40	60
"	" 4.5	6.0	94.0	"	" 1.2	36	64
"	" 2.3	7.0	93.0	"	" 1.2	39	61
"	" 4.0	7.0	93.0	"	" 1.2	28	72
"	" 2.4	6.0	94.0	"	Exophthalmos, 3.8	16	84
Mayer	" 1.5	40.0	60.0	"	" 3.8	10	90

Table I shows the great variation in the ratio of the urinary and fecal calcium output in normal as well as pathological conditions.

A most important contribution to our knowledge of the course of events in calcium metabolism when a sudden and severe drain is made upon the calcium of the body was made by McCallum and Voegtlin[23] in their article on the "Extirpation of the Parathyroid." They found that after this operation dogs developed symptoms of tetany which disappeared when calcium was administered; analyses of the tissues showed that there was a decrease of the calcium content of the soft parts and the blood. Since the bones were not obviously affected the condition was one in which their calcium was not available, probably because the whole process was too acute.

This consideration of the literature allows the following conclusions to be drawn as far as one may conclude anything from records which cover so short a period as many of those quoted do. Absorption is an unapproachable problem. The physiological requirement is about 0.014 gram CaO per kilo daily for an adult. Underfeeding of calcium is followed by a calcium loss. A diet rich in calcium is followed by a calcium retenion. Acidosis is accompanied by a calcium loss.

Since the thyroid gland is so closely associated with metabolism phenomena and cases of exophthalmic goitre were easily obtainable, it seemed advisable to investigate the calcium balance in this condition. The literature of the metabolism of Basedow's disease is given fully in von Noorden's text-book; a considerable number of cases have been followed for the nitrogen metabolism, and the results have been identical; namely, that in most though not all of the cases there is a loss of nitrogen in the later and more severe stages of the disease. No change was found in the chlorides and the phosphates were inconstant, and in no cases had the calcium been determined.

Three weeks was decided upon as the longest time feasible for following the metabolism of a hospital patient; as it was impossible to keep a person on the same diet daily for that length of time, a rotating diet was devised, which contained the same amount of calcium daily, and also as little as possible, that the effect of the calcium salt administered might be evident. The diet consisted of 30 grams of oatmeal weighed raw, 150 grams of bread, 90 grams of butter, 3 grams of salt, 50 grams of sugar, 50 grams of cream, one cup of coffee, 1500 c.c. of water daily; 150 grams of beef, 150 grams of potatoes, 100 grams of spinach; or 150 grams of lamb, 150 grams of rice, 100 grams of peas; or 200 grams of chicken, 150 grams of potatoes, 100 grams of cauliflower on successive days, and repeated in regular order through the weeks of the work.

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[23] Jour. Exper. Med., 1909.

At the end of the day, when the residues were weighed out, one-half the quantity actually consumed was weighed for analysis, put through a grinder into an evaporating dish, together with the washings of the grinder itself, and evaporated to dryness on a steam oven and dried at 110° for thirty-six hours, weighed and powdered. The mixture contained six articles daily; the butter was analyzed separately. The same diet was used in both cases. A preliminary period of four days in which no calcium was given preceded the administration of the calcium, which was given in the form of the lactate, and in this first case in doses of 5 grams daily, in capsules. The feces were marked off at the end of four, six, five, and four days, with decalcified charcoal, for the purpose of separating the preliminary period from the rest of the time, and of obtaining the balance at intervals through the calcium taking time. The urine was collected from 7 A.M. to 7 A.M., and all estimations were made on the same day that the material was sent to the laboratory.

The first patient was aged thirty-one years, single, occupied a separate room, and was attended by a special nurse. Physical examination revealed no abnormality, and her difficulty in walking for which she entered the hospital was diagnosticated by Prof. Barker as hysterical, and this was subsequently confirmed by her recovery. Unfortunately she was very constipated, and a plain water enema was given daily; in addition to this a purgative was given once during each period (2 drams of castor oil). Her weight, one hundred and forty-eight pounds, was the same at the end as at the beginning of the experiment. Table II shows the food nitrogen and calcium and the urine and feces; also the total acidity, the phosphates, and the ammonia of the urine. The nitrogen was estimated by the method of Kjeldahl, the ammonia by the Folin method, the phosphates by titration with uranium acetate, the total acidity by titration with one-tenth normal NaOH solution with phenolphthalein as an indicator, the calcium was brought down in a solution of acetic acid as the oxalate and titrated as calcium with potassium permanganate.

An accident to the tray on which the patient's meals were served, on the ninth day of the experiment, makes the intake of that day a little uncertain; but the calcium of the food was so small a part of the whole amount that no great error could have occurred. The preliminary period showed a loss of calcium, the first and second periods of the calcium-taking time a slight retention; the urinary calcium was of a higher daily average than the calcium of the food; in the last period there was a slight loss. The patient had been in the hospital three weeks, and had taken considerable milk in that time, so that the observation follows a period of calcium-rich diet.

TABLE II.

FOOD.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Nitrogen	10.31	8.09	9.15	14.35	11.40	13.80	9.66	10.81	10.96	9.25	12.68	15.07	9.65	8.17	13.49	9.21	13.85	12.70	12.81
					0.909	0.909	0.909	0.909	0.909	0.909	0.909	0.909	0.909	0.909	0.909	0.909	0.909	0.909	0.909
Calcium	0.3547	0.2359	0.4192	0.3126	0.2022	0.2299	0.4356	0.2862	0.1145	0.3644	0.2359	0.2337	0.4332	0.2283	0.3648	0.3648	0.2328	0.2268	0.2596

URINE.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Quantity	1820 c.c.	1090	1300	970	1340	1070	1052	1100	900	1249	910	1225	1545	710	919	1420	1350	1565	1000
Acidity	473	452	318	300	192	214	115	177	207	124	182	214	123	117	188	142	162	125	220
Ammonia	0.8635	0.982	0.7403	0.6812	1.001	0.7276	0.4471	0.4320	0.5202	0.4352	0.4486	0.5915	0.3939	0.6095	0.4140	0.4586	0.5622	0.385	0.595
Phosphates	2.82	2.25	1.40	0.714	0.995	1.071	1.01	0.907	1.118	1.29	0.930	1.06	1.13	1.17	1.16	1.24	1.09	0.929	9.57
Nitrogen	10.43	14.64	9.35	9.72	8.12	9.73	8.02	6.57	7.75	8.28	7.02	8.37	7.31	7.36	9.69	8.94	9.90	8.76	8.23
Calcium	0.5619	0.4327	0.2534	0.2562	0.3762	0.3802	0.4099	0.3921	0.3301	0.3386	0.4306	0.4127	0.4219	0.3251	0.3818	0.3839	0.3557	0.2706	0.3901

FECES.

	1–4	5–10	11–15	16–19
Nitrogen	5.4138	4.8069	4.0534	5.6501
Calcium	3.2104	3.7913	3.0528	3.7883
Quantity	79 grams	90 grams	70 grams	91 grams

BALANCES.

	1–4	5–10	11–15	16–19
Nitrogen	—7.6569	+12.5995	+15.2443	+7.0925
Calcium	—3.392	+ 1.06	+ 1.0762	—0.4695

Total nitrogen, +27.2792. Total calcium, +1.660 (in calcium-taking period). Total calcium, —1.7315 (in whole time).

The second patient was aged thirty-five years, and weighed 106 pounds; she had a marked case of exophthalmic goitre; there was a large tumor of the thyroid, a pulse rate of 130 to the minute when she entered the hospital, a fine tremor of the fingers, and considerable exophthalmos; there was little sweating; the heart, lungs, and abdomen showed no abnormality; the urine was negative, and the temperature was normal. This patient had also been in the hospital for some time, and had had milk daily. She was given the same diet as the first patient and 20 grams of calcium lactate daily in water flavored with lemon juice. Her pulse rate was 100 to the minute when the work was begun, and no change took place in this; in general, her condition appeared the same; the patient herself thought she was the same, except that an unpleasant sense of constriction had disappeared from about the throat. On the third day of the second period, the first of the calcium taking, the stools of this patient became very green, and remained so through the whole of the time; but were normal as soon as the calcium was stopped. When the time was about half over we learned that the patient was pregnant, in the first weeks. On the two days indicated by a plus sign the urine was partly lost into the feces, so that, though the whole balance is accurate, the ratio of the urinary and fecal output is lost. Subsequently the patient was operated on by Dr. Halsted and made an uninterrupted recovery, and left the hospital much improved. In this case (Table III) the nitrogen balance was positive in the first period by 5.3 grams, in the second period there was a loss of 4.8 grams, and in the third a loss of 11.4 grams, followed by a retention of 3.4 grams; in the whole time a loss of 7 grams and one pound in weight; the patient was hungry most of the time, which she said was usual with her in the early stages of pregnancy. The calcium balance was negative in the first period and showed a retention in the second of 3.7 grams CaO, followed by a loss of 6.6 grams and in the last period a loss of 0.45 gram CaO; there was a total loss of 5.4 grams CaO. That such a loss of calcium is not an inseparable accompaniment of Basedow's disease is shown by the calcium balance of a patient who suffered with a severe case of exophthalmic goitre; she was aged forty years, and was kept on a diet of 1 liter of milk, 150 grams of beef, and 50 grams of bread; there was a retention of nitrogen; the urinary calcium was low, probably because of a renal insufficiency; the observation lasted eight days; the ammonia and total acidity were normal:

CaO intake.	Urine.	Feces.	Total output.	Balance.
24.48 grams	1.0437	17.5	18.54	+7.94

In this case there was a retention of nearly 1 gram a day on a less intake of CaO in the form of milk.

Shown graphically, the nitrogen and calcium curves in the case in which the calcium lactate was used is as in Charts I and II.

TABLE III.

FOOD.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Nitrogen	12.72	10.21	13.30	9.74	10.20	12.60	12.65	8.64	15.11	9.47	10.83	12.60	10.93	10.45	12.50	12.56	14.40	13.80	11.33
					3.636	3.636	3.636	3.636	3.636	3.636	3.636	3.636	3.636	3.636	3.636	3.636	3.636	3.636	3.636
Calcium	0.2361	0.3832	0.2520	0.2529	0.2901	0.2500	0.2084	0.3987	0.2934	0.2494	0.3332	0.2282	0.2157	0.3447	0.2455	0.2165	0.3499	0.2487	0.2325
URINE.																			
Quantity	670	1480	910	770	760	700	520	1330	860	1660	1060	960	1260	1020	865	1060	810	1485	1420
Acidity	323	148	264	269	315	255	187	234	133	192	79	86	163	86	246	276	129	141	
Ammonia	0.6052	...	0.8315	0.8737	0.9011	0.8181	0.8331	0.7743	0.5957	0.986	1.103	0.7711	0.6693	0.7326	0.5531	0.8284	0.8185	1.016	
Phosphates	1.519	...	1.361	1.55	1.27	1.05	0.729	1.26	0.94	1.28	0.93	0.89	1.21	0.88	1.03	1.21	0.82	1.40	
Nitrogen	8.30	5.05	9.75	9.90	10.40	10.68	8.63	12.88	10.26	13.59	14.31	10.14	14.77	10.24	11.01	14.59	10.17	11.75	5.21
Calcium	0.1485	0.1891	0.2563	0.3452	0.4915	0.4856	0.2216	0.7942	0.5391	0.5233	0.4334	0.4448	0.7008	0.3589	0.5638	0.4202	0.5610	0.7065	0.2830
FECES.																			
Nitrogen	7.6476				6.7468						8.3377					5.9071			
Calcium	2.3387				16.6822						23.6549					14.0739			
Amount	143 grams				192 grams						215 grams					118 grams			
BALANCES.																			
Nitrogen	+5.3473				—4.8213						—11.4905					+3.459			
Calcium	—2.1536				+3.7685						—6.6093					—0.4560			

Total nitrogen, —7.5055. Total calcium CaO, —3.2968 (calcium-taking period). Total calcium CaO, —5.4504 (whole time).

From left to right one square represents a day. The base line is equilibrium. In the nitrogen it is about 11 grams; in the calcium, in the preliminary period, it is 0.22 gram and the rest of the time 3.8 grams CaO; in both substances each square above or below the base line is 1 gram. Evidently the second and third periods are coincident with such a wave of metabolism activity as others have observed in this disease, or the loss may be associated with the pregnancy.

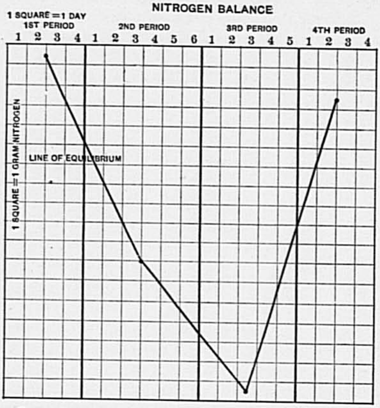

Chart I.—Illustrating the nitrogen balance in Case II.

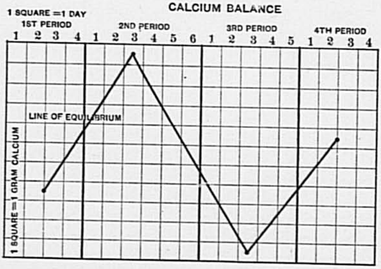

Chart II.—Illustrating the calcium balance in Case II.

Whatever may be the cause of the stimulation of the metabolism, the parallelism of the nitrogen and the calcium is apparent. The loss of the latter substance in the preliminary period is due to the extremely small intake, the usual picture of underfeeding, and that the retention is much smaller than it would be in a normal individual in nitrogen equilibrium I have no doubt; unfortunately both attempts to establish this point were unavailing, since there were losses in the collections that stopped the work. The influence of the amount of calcium taken and the form in which it is ingested upon the retention of calcium and the relation of the nitrogen balance to this may be seen by arranging the results of the work done on calcium overfeeding in the form of a table (Table IV):

TABLE IV.

Author.	Subject.	Form.	Amount. Grams.	Daily Retention in grams.	Retention. Per cent.	N balance in grams.	No. of days.
Herxheimer	Himself	$CaCO_3$	8.0 CaO_3	1.9	23	4.3	8
Kaufmann	Normal	Milk	6.0 "	2.2	38	34.2	7
"	"	"	4.5 "	2.0	47	56.6	10
Rumpf	Ulc. vent.	"	3.3 "	1.8	56		
King	Arthritis	Folin	4.5 "	1.9	41	5.8	5
Hirsler	Arteriosclerosis	Milk	6.5 Ca	1.5	23	14.4	6
Moraczewski	Diabetes	Cal. phos.	5.3 "	1.8	33	2.39	7
"	"	" "	2.3 "	0.4	10	—18.9	5
"	Chlorosis	" "	5.0 "	3.9	78	42.3	5
"	"	" "	5.3 "	4.1	75	24.1	5
"	Carc. vent.	" "	4.3 "	3.1	74	4.3	11
Ott	Phthisis	Milk	4.4 "	0.6	14	0.05	4
"	"	"	6.1 "	0.7	11	—2.39	4
"	"	"	6.0 "	0.1	3	—2.63	4
"	"	"	4.5 "	0.5	11	—3.36	4
"	"	"	4.5 "	0.1	4	—0.08	4
"	"	"	2.3 "	0.1	5	10.0	8
"	"	"	4.0 "	0.2	7	—2.97	3
"	"	"	2.4 "	...	..	0.08	6

The variety of conditions observed and the different amounts and forms of administration used allow but few conclusions to be drawn from this table. It is interesting to note the constancy of the daily retention on an intake of 4 to 6 grams of CaO daily in the form of milk; the agreement of the normal and pathological subjects of observation except diabetes and phthisis; the greater retention of the phosphate; and the parallelism of the nitrogen and calcium balances. It is evident that a loss of calcium may be prevented by a sufficient intake even when there is a large negative balance of nitrogen; this is seen in the second period of the administration of the phosphate in the case of diabetes and in the series of phthisical subjects. That this narrow margin of a positive balance is attained at the price of a considerable diminution of a possible retention is seen by a comparison with the retention in those cases on the same intake which have a positive nitrogen balance. Recently, Mayer[24] has shown that a positive calcium balance occurred without exception in a series of phthisical subjects on an intake of 1.5 to 2 grams CaO in a day when there was a positive nitrogen balance. Von Wendt showed in a physiological case that with a sufficient though moderate nitrogen intake there was a retention of nitrogen together with a loss of calcium with a calcium underfeeding; also that there was a calcium retention on a moderate intake associated with a nitrogen loss due to nitrogen underfeeding. Renvall had an enormous loss of nitrogen through the whole time of his experiment, and was in calcium equilibrium at an intake of 0.9 gram and retained calcium when he made the small additions of the carbonate. He attributed the loss of nitrogen to the diet he was using, and noted that the fecal nitrogen was unduly high, a condition of underfeeding practically. Thus, we see that while the nitrogen and calcium balances may rise and fall together in a general way, it is a phenomenon of disease rather than of health, and has been found to occur in phthisis, diabetes, and exophthalmic goitre; though even here the calcium balance may be made to be positive with a sufficient intake, though not without evidence of the tendency to loss.

In regard to the cases recorded here, the first experiment shows that the lactate is an easily absorbable salt, as the urinary output is higher than the calcium content of the food. The case of exophthalmos shows a retention of only 15 per cent. of the intake in the first period of the administration of the lactate as compared with 38 per cent. and 40 per cent. retentions in other cases in which milk was used containing approximately the same amount of calcium in terms of CaO, and in which there was also a retention of nitrogen. In the next period, with the loss of 11 grams of nitrogen, there was a loss of 6.6 grams of CaO, while in the case of diabetes there was a slight positive balance, though the intake was 2.3 grams of CaO only and the nitrogen loss was 18 grams. What part of this wide difference is due to the pathological conditions and what to the salts used must be determined by further work.

CONCLUSIONS. Calcium given in the form of the lactate enters into the general metabolism or allows the calcium already present in the body to be utilized without loss. Given by the mouth there is no toxic effect from the administration of 20 grams of calcium lactate over a period of fifteen days.

The calcium metabolism of Basedow's disease shows no special peculiarity; it runs parallel with the nitrogen, and in those periods of the disease in which there is a loss of nitrogen there is also a loss of calcium—a parallelism which is found in other pathological conditions.

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[24] Deut. Archiv f. klin. Med., 1907.

My thanks are due to Prof. Barker for permission to work in his laboratory and with his patients; to Dr. Voegtlin for the preliminary instruction which made it possible ultimately to undertake this work and his interest and advice throughout; to the nurses in charge of the patients, the Misses Richardson, French, and Allen, and to Miss Wilder, of the diet school, through the long and trying period of the weighing.

HOW FAR IS HEREDITY A CAUSE OF AURAL DISEASE?

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Some five years ago I presented to the Section on Otology of the College of Physicians, but did not publish, a brief note combating the claims made by some authors as to hereditary influences in the causation of ear disease. The subject has considerable practical importance, since we do not wish to waste time upon cases which are foredoomed to afford no success; but also because many people, under an erroneous impression that they are victims of inherited deafness, fail to seek relief at the hands of the surgeon while it is still possible to obtain it. The cure of the chronic catarrhal forms of deafness, not to speak of so-called "otosclerosis," is hard enough at best, and discouragement is all too easy without bringing in imaginary heredity to darken the prospect; yet the claimed bearing of inheritance often seems so far-fetched, if not preposterous, that I again offer a word in opposition,

Just as before I cited two cases of penetration of the drumhead by a twig, and jestingly asked what but heredity had produced this rare accident in cousins, so now it is the close parallelism of conditions in father and son which serves as a text for my remarks. A clergyman came to me nine years ago with Shrapnell perforation and cholesteatoma on the right side and marked defect of hearing from catarrhal deafness on the left. These have yielded none too perfectly to treatment, so that he is still under periodic care, with some tendency to brief recurrence of suppuration in his right antrum, where skin masses collect at intervals until perhaps there is new polyp growth as Nature's protest and effort to expel the collection. Most of the time he is so free from trouble as to be prone to neglect the needed care, while his hearing remains about double what it was on coming, although still imperfect in each ear.

Recently he brought his father because of decrease in hearing, and I found large cholesteatomatous masses protruding from his right antrum and attic, removal of which showed a virtual tympanic exenteration spontaneously done, differing from the